REMARKS

No amendments to the claims have been made as a result of this amendment. Claims 9-11, 13-16 and 19-29 are currently pending.

Rejection of Claims 9, 10, 11, 13, 15, 16, 19-26, 28 and 29 Under 35 U.S.C. §102(a) over Tse et al.

In the Office Action, claims 9, 10, 11, 13, 15, 16, 19-26, 28 and 29 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Tse et al. (WO 94/26787).

The effective date of the Tse et al. patent application is November 24, 1994. Accordingly, applicants submit a Declaration pursuant to 37 C.F.R. §1.131 executed by all of the inventors, namely Dr. Leon WMM Terstappen and Dr. Ton Logtenberg, to antedate the Tse et al. reference for claims 9-11, 13-16, 19 and 22-29. Applicants also present arguments below refuting the rejection of claims 20 and 21 over Tse et al.

Rule 131 Declaration Antedating Tse et al.

The Rule 131 Declaration establishes both conception and reduction to practice prior to the November 24, 1994 effective date of Tse et al. A claim chart is attached as Exhibit A. The claim chart correlates each element of the claims with information sworn to by the inventors. The relevant portions of the information are provided in Exhibits B, C, D1, D2 and E.

The evidence cited in the claim chart and relied upon to demonstrate conception and reduction come from three different sources. The dates have been removed from the documents. Both Dr. Terstappen and Dr. Logtenberg state that all three sources of information used to show conception and reduction to practice antedate the November 24, 1994 effective date of the Tse et al. reference. See paragraphs 7, 8 and 10 of the Rule 131 Declaration.

The first source of information relied upon in the claim chart is a memorandum from Dr. Terstappen to various individuals at Becton Dickinson located in New Jersey. The memorandum and the materials attached to the memorandum are attached as Exhibit B.

The memorandum in Exhibit B is divided into five sections and describes the materials attached to the memorandum. The materials attached to the memorandum, in turn, are numbered by section (e.g., B-I, B-II, B-III, B-IV and BV) and page number according to the section and page number the materials are referred to in the memorandum.

Section I of the material attached to the memorandum (eight pages) explains how the library of antibodies used in the method of the invention was created. Page 3 of Section I demonstrates that the phage libraries contain antibody molecules expressed on the phages. Section II of the materials (fourteen pages, although the memorandum refers to thirteen pages) demonstrates the selection of phage monoclonal antibodies by cell sorting. This cell sorting includes the steps of incubating the phage antibody library with a heterogeneous cell population containing non-target and target cells in a heterogeneous mixture, separating the target cells and recovering the phage particles. These steps are shown in the first page in Section II. The remaining pages in Section II show the sort criteria used, the number of phages recovered from sorted blood cells, and the staining profile and characterization of various phage monoclonal antibodies. Section III of the materials attached to the memorandum consists of five pages which describe various applications of the technology. Section V discloses the production of antibodies using the library of phage particles.

The second source of evidence for conception and reduction to practice before the effective date of the Tse et al reference is from a notebook generated by John deKruif from laboratory experiments performed under the direction and supervision of the inventors. These experiments were performed at Becton Dickinson Immunocytometry Systems (BDIS) in California before the date of the memorandum outlined above. A copy of the notebook pages

relied upon in the claim chart (the first four pages of the notebook) are attached hereto as Exhibit C.

Dr. Logtenberg has provided a more detailed description of page 3 of the notebook from Exhibit C. This detailed description provided by Dr. Logtenberg is attached as Exhibit D1. James F. Harrington, one of applicants' representatives (and a colleague of mine at Hoffmann & Baron, LLP), prepared a summary of Dr. Logtenberg's detailed description. The summary is attached as Exhibit D2. Dr. Terstappen and Dr. Logtenberg have attested to the fact that Exhibits D1 and D2 contain accurate descriptions of the experiment recorded at page 3 of the notebook (Exhibit C).

Dr. Logtenberg's description of the experiment on page 3 of the notebook provides a clear demonstration of the reduction to practice of the method of the invention. For example, with regards to independent claim 9, providing a library of antibody fragments expressed on the surface of phage particles is recited in step (a), incubating the phage antibody library with a heterogeneous cell population containing non-target cells and target cells is recited in step (b), separating the target cells bound by phage particles from unbound target cells is recited in step (c), and recovering the bound target cells is recited in step (d). The results shown on page 4 from the notebook demonstrate the number of bacterial colonies obtained in each experiment.

The third source of evidence relied upon in the claim chart to show conception and reduction to practice before the effective date of Tse et al. are the results of additional studies performed at the BDIS facility in California. These materials are attached hereto as Exhibit E. The experiments demonstrate the isolation, in accordance with the invention, of single chain antibodies binding to cells, as shown by the various staining patterns obtained. The phage antibodies used for these experiments are mentioned in the table within Exhibit E. The names used for these antibodies are found in the staining diagrams on the subsequent pages.

Summary of Antedating Tse et al.

The inventive concept is related to the inventors' appreciation of using phage display library technology to isolate antibodies directed to surface markers (e.g., antigens) on subpopulations of cells in a heterogeneous mixture containing non-target and target cells. Dr. Terstappen and Dr. Logtenberg establishes in the declaration that the inventive concept was conceived and reduced to practice before the November 24, 1994 effective date of Tse, et al. See paragraph 11 of the Rule 131 Declaration.

The conception of the method of the invention is most clearly shown by the material in Exhibit B, Sections I and II. On Page 4 of Section I, "phage antibody display" is described as the "expression of fragments of antibody molecules (scFv / Fab) on the surface of filamentous bacteriophages." Page 8 of Section I, discloses that "biomolecular interactions with the target structure allows the selection of specific phage antibodies."

Section II, page 1 of the materials attached as Exhibit B demonstrates selection of phage Mab's by incubating the phage antibody with the target cells, separating the target cells and phage particles associated therewith from phage particles not associated with the target cells, and recovering the phage particles associated with the target cells.

The staining profiles attached to Section II of Exhibit B, and the additional laboratory studies attached as Exhibits C and E demonstrate that the invention was reduced to practice before November 24, 1994. See above.

Therefore, as demonstrated in the claim chart and attested to by Dr. Terstappen and Dr. Logtenberg, the evidence submitted demonstrates conception and reduction to practice before the November 24, 1994 effective date of the Tse et al. reference. Accordingly, applicants have established conception and reduction to practice of claims 9, 10, 11, 13, 15, 16, 19, 22-26, 28 and 29 before the November 24, 1994 effective date of Tse et al.

Refuting Rejection of Claims 20 and 21 By Tse et al.

Even if Tse et al. constituted relevant prior art, and applicants insist it does not (see above), Tse et al. does not render the pending claims anticipated. Applicants provide below arguments to refute the rejection of claims 20 and 21 over Tse et al.

According to the examiner, Tse et al. disclose that the cells act as solid supports. The examiner cites page 2, lines 23-24 of Tse et al. Thus the examiner contends that applicants' claims that read on the non-target antigens bound to solid supports are anticipated by Tse et al.

Applicants respectfully disagree. In fact, Tse et al. disclose on page 2, lines 23-24 that the membranes of the target cells can be considered a solid support. Nowhere in Tse et al. is there any disclosure that the non-target antigens are immobilized. In contrast, claims 20 and 21 of the present invention are directed to immobilization of non-target antigens. Accordingly, claims 20 and 21 are not anticipated by the Tse et al. reference.

Conclusion of Rejection of Claims under 35 U.S.C. §102(a) over Tse et al.

Applicants have established conception and reduction to practice of claims 9-11, 13-16, 19 and 22-29 before the November 24, 1994 effective date of the Tse et al. reference. In addition applicants have also provided arguments refuting the rejection of claims 20 and 21. Accordingly, the rejection of the claims under §102(a) should be withdrawn.

Rejection of Claims 9-11, 13-16 and 19-26 Under 35 U.S.C. §103(a) over Tse et al. in view of Verwer et al.

Claims 9-11, 13-16 and 19-26 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Tse et al. in view of Verwer et al. (EP 0610774A1). The examiner concedes that Tse et al. do not specifically teach the fluorochromes listed in claims 14 and 27.

To rectify the deficiency, the examiner cites Verwer et al. According to the examiner, Verwer et al. disclose a method of flow cytometry with cells labeled with FITC or PE.

As stated above, applicants have established that the primary reference, i.e. Tse et al., was not properly cited against the claims. The disclosure of the secondary reference, i.e. Verwer et al., is not sufficient to sustain the rejection by itself. Accordingly, the rejection should be withdrawn.

Double Patenting Rejection

Claims 9-11, 13-16 and 19-26 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,265,150 in view of Tse et al.

The Examiner indicates that the filing of Terminal Disclaimers may be used to overcome this rejection. Accordingly, a Terminal Disclaimer in compliance with 37 CRF §1.321(c) is submitted herewith. It is respectfully submitted that this Terminal Disclaimer is in proper form and overcomes the double patenting rejection.

In view of the above remarks, allowance of pending claims 9-11, 13-16 and 19-29 is earnestly requested. If the examiner has any questions regarding this amendment, the examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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